Medication Deprescribing

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Disclosures

- I am employed at Prescriby Health

Objectives

- Review the principles of deprescribing
- Describe success rates in deprescribing medications for opioid use disorder
- Discuss optimal strategies in deprescribing benzodiazepines/Z-drugs
- Briefly address the challenges of antidepressant deprescribing

Principles of Deprescribing

Deprescribing

The planned and supervised process of reducing or stopping medication for which existing harms outweigh benefits

Reasons to deprescribe

- Adverse effects – harms outweigh benefits
- Loss of efficacy
- Condition has resolved
- Polypharmacy
- High-dose prescribing
- Patient preference

Barriers to deprescribing

- Psychologic/physiologic factors
  - Stressful life circumstances
  - Poor past experiences with discontinuation
  - Lack of effective coping strategies
  - Physical dependence
- Belief that a long-term condition requires long-term treatment
- Fears
  - Fear of relapse and withdrawal symptoms
- Personal Notions
  - Self-identify as ‘disabled’
  - Stopping is a threat to stability
  - Cure is not possible

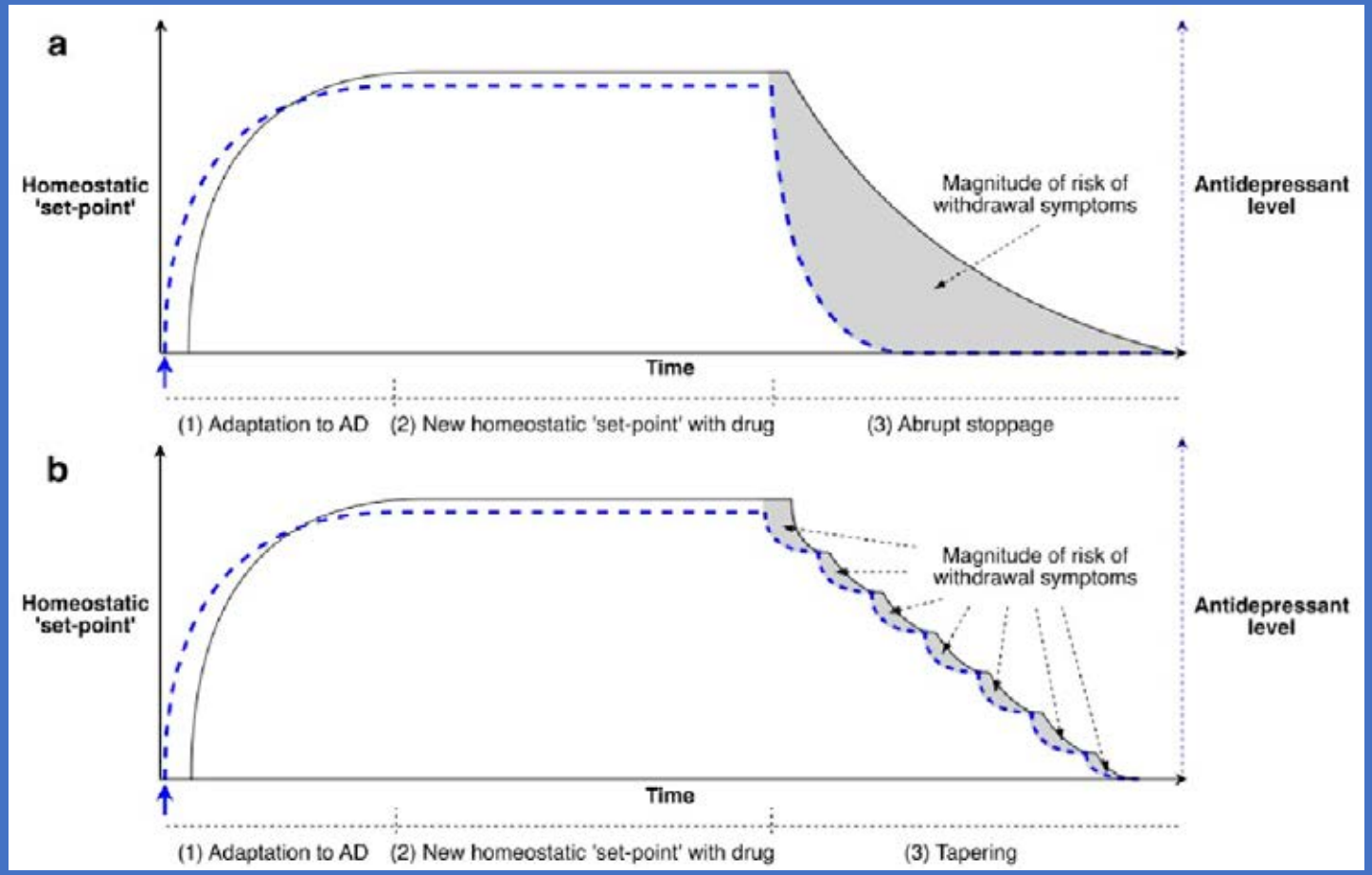
Dependence vs Addiction

- Sometimes used interchangeably
- Dependence
  - Physical state that develops as a result of a physiological adaptation in response to repeated drug use, manifested by withdrawal symptoms after abrupt discontinuation
  - Mainly physiologic
- Addiction
  - Compulsive, uncontrollable substance seeking despite harmful consequences
  - Involves behavioral and emotional factors

Deprescribing Guidelines

- Taper gradually
  - Over months rather than weeks – sometimes longer
- Taper at a rate the individual finds tolerable
- Taper in a hyperbolic pattern
- Taper to low doses before stopping

Abrupt Cessation vs Taper

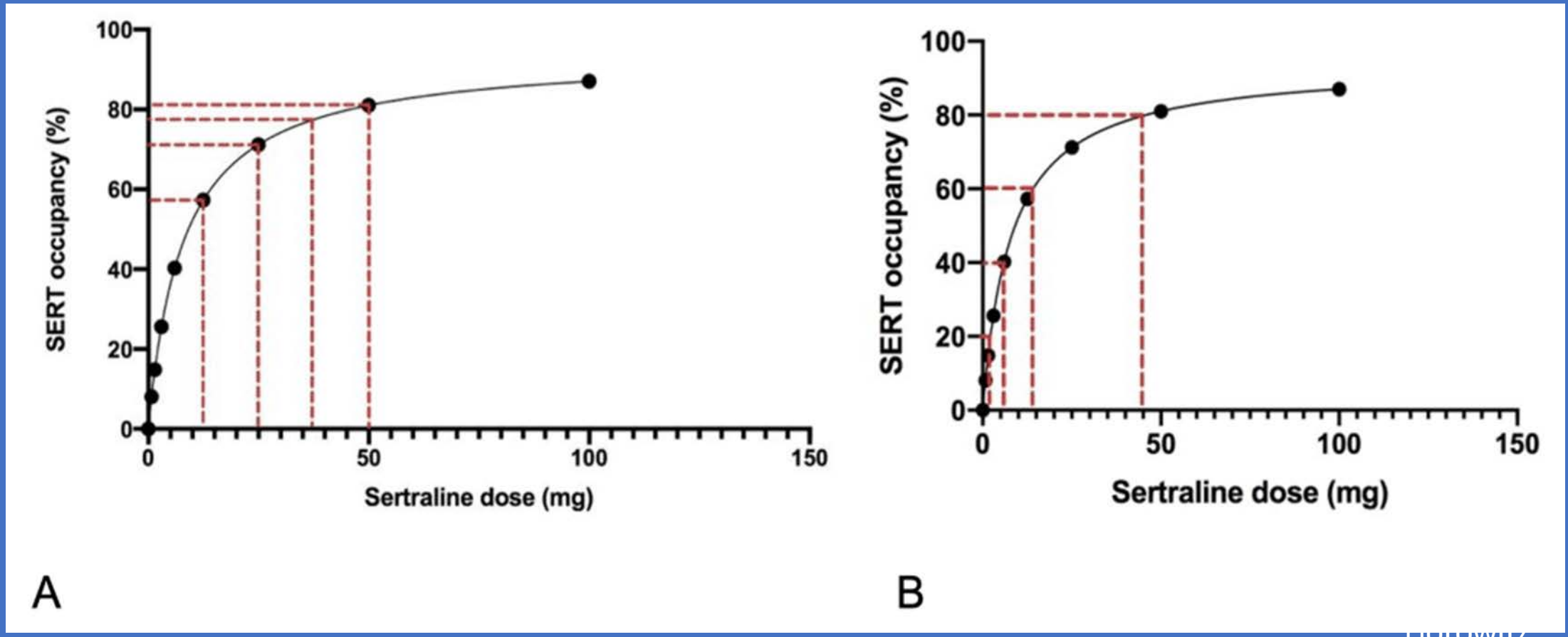


Horowitz

Tapering Strategies

Linear/Conventional Taper

Hyperbolic Taper



Horowitz

Hyperbolic Tapering Example

STEP	RO (%)	DOSE (MG)	VOLUME
1	88	300	Use tablets/capsules
2	87	150	Use tablets/capsules
3	84	75	Use tablets/capsules
4	78	37.5	Use tablets/capsules
Switch to venlafaxine 7.5 mg/mL solution*			
5	68	18	1.2 mL (twice daily)**
6	59	10.8	0.72 mL (twice daily)
7	49	6.9	0.46 mL (twice daily)
8	39	4.5	0.3 mL (twice daily)
Switch to venlafaxine 0.75 mg/mL dilution*			
9	29	2.85	1.9 mL (twice daily)
10	20	1.65	1.1 mL (twice daily)
11	10	0.75	0.5 mL (twice daily)
12	0	0	Stop taper

Horowitz

Evidence for hyperbolic tapering

- Study involving 824 participants
  - Most prescribed antidepressants for 5-10 years
  - Most common medications = venlafaxine and paroxetine
  - 71% unable to successfully taper by conventional means
    - Of these individuals, 72% successfully tapered off using hyperbolic reduction
  - Final dose
    - Paroxetine – 0.5mg
    - Venlafaxine – 1mg

Withdrawal vs Relapse

- Withdrawal
  - AKA discontinuation syndrome
  - Involves physical and psychological symptoms occurring after reducing or stopping medication

- Relapse
  - Return of original symptoms (e.g., depression, anxiety)

Distinguishing Withdrawal from Relapse

- Time of Onset
  - Withdrawal – occurs hours or days after skipping, reducing, or stopping the medication
    - Can last months or years
  - Relapse – Onset of weeks to months after medication cessation

Distinguishing Withdrawal from Relapse

- Presence of distinctive symptoms
  - Withdrawal
    - “I’ve never felt this way”
    - Physical + psychological symptoms
    - Physical symptoms – nausea, dizziness, ‘brain zaps’
  - Relapse
    - Symptoms similar to original condition
- Response to reinstatement
  - Withdrawal – more rapid resolution with reinstatement (within a few days)

Misdiagnosis of Withdrawal

- **Mis-diagnosed as new-onset medical condition**
  - Functional neurologic disorder
  - Chronic Fatigue Syndrome
  - Malingering

- **Mis-diagnosed as a mental health condition**
  - Agitated depression
  - Bipolar disorder
  - Psychosis

Rebound Symptoms

Symptoms present in baseline condition with greater severity in withdrawal

Delayed onset of withdrawal symptoms

- Drugs with long half lives
  - I.e. fluoxetine
    - Long elimination half-life of active metabolite norfluoxetine (7-15 days)

- Withdrawal symptoms from short half-live medications can emerge weeks after discontinuation
  - In one study, mean time to onset of withdrawal symptoms following discontinuation was 4.5 weeks

Vigilance should be maintained for weeks after medication cessation – particularly when physical symptoms are reported

Withdrawal Akathisia

- Most often recognized in antipsychotic use, but has also been observed in antidepressants and benzodiazepines

- One of the most distressing consequences of withdrawal
- Pathophysiology poorly understood
- Characterized by:
  - Severe agitation
  - Restlessness
  - Sense of terror
- Can be mis-diagnosed
  - Manic state, anxiety disorder, ADHD, drug-seeking behavior
- Associated with suicidality

Protracted Withdrawal Syndrome

- aka ‘PAWS’

- Symptoms persist beyond 4-6 weeks
- Can last weeks to as long as 12 months
- Occurs in 10-25% of people
- Characterized by ‘waves’ (severe symptoms) and ‘windows’ (relative freedom from symptoms)

Protracted Withdrawal Syndrome

- Anxiety
- Cognitive Impairment
- Depression
- Insomnia
- Formication
  - False sensation of insects crawling on or under the skin
- Motor symptoms
- Tinnitus

- Study of 1200 individuals seeking peer support for stopping benzodiazepines
  - >1/2 – affected marriage
  - ~½ lost job or became unable to work
  - ~½ had either attempted or contemplated suicide

Missed doses causing withdrawal symptoms

- If taking a medication in the first few weeks, doses that are accidently missed or skipped may result in withdrawal symptoms
- Can be reported as sudden onset psychologic or physical symptoms
  - Dizziness
  - Headache
  - Mood changes
- Departures from regular dosing are common
  - Irregular dosing in 50% or more of individuals
- May lead to inappropriate medical care and prescriptions

Deprescribing Buprenorphine

Ling et. Al, 2009

- Randomized open label study
- Primary Outcome = % illicit opioid-free urine specimens at end of taper

- 7 day taper - 44% (*n* = 255) provided illicit opioid-free specimens
- 28 day taper - 30% (*n* = 261) provided illicit opioid-free specimens

- No differences for 1-month and 3-month follow-up rates
  - 7-day = 18% and 12% (1 month and 3 month)
  - 28-day = 18% and 13% (1 month and 3 month)

More rapid discontinuation in the 7-day taper did NOT result in greater withdrawal symptoms or craving compared to 28-day taper

Bozinoff et. Al, 2022

- Retrospective cohort study (N = 5774)
- Primary Outcome = Prescribing characteristics associated with opioid overdose following buprenorphine taper

- Time to taper initiation
  - >1 year = 6.73 ODs per 100 person-years
  - 1 year or less = 10.35 ODs per 100 person-years

- Rate of decrease
  - 2 mg decrease per month, 6.95 overdoses per 100 person-years
  - >2 to 4mg decrease per month, 11.48 overdoses per 100 person-years
  - >4 mg decrease per month, 17.27 overdoses per 100 person-years

- # of decrease days
  - 1.75% or less of days – 5.87 overdoses per 100 person years
  - 3.5% or more days = 13.87 overdoses per 100 person years

Buprenorphine tapers undertaken after at least 1 year of therapy, a slower rate of taper, and a lower percentage of days during which the dose was decreasing were associated with a significantly lower risk of opioid overdose, regardless of taper duration

Weinstein et. Al, 2018

- 12 year retrospective cohort study
- Primary Outcome = completion of taper off buprenorphine

- N = 1308 patients with median follow-up time 316 days
- 48 patients (15%) were observed to taper off buprenorphine during the study period
  - 45.8% (22/48) were medically supervised
  - 13 of these 48 patients subsequently, reengaged in treatment
    - Estimated proportion 61% (95% CI: 27%-96%), based on Kaplan-Meier analyses

A minority of participants had a documented taper. Among those who tapered, more than half did so unsupervised by the clinic and a majority of those who tapered off returned to buprenorphine treatment within two years

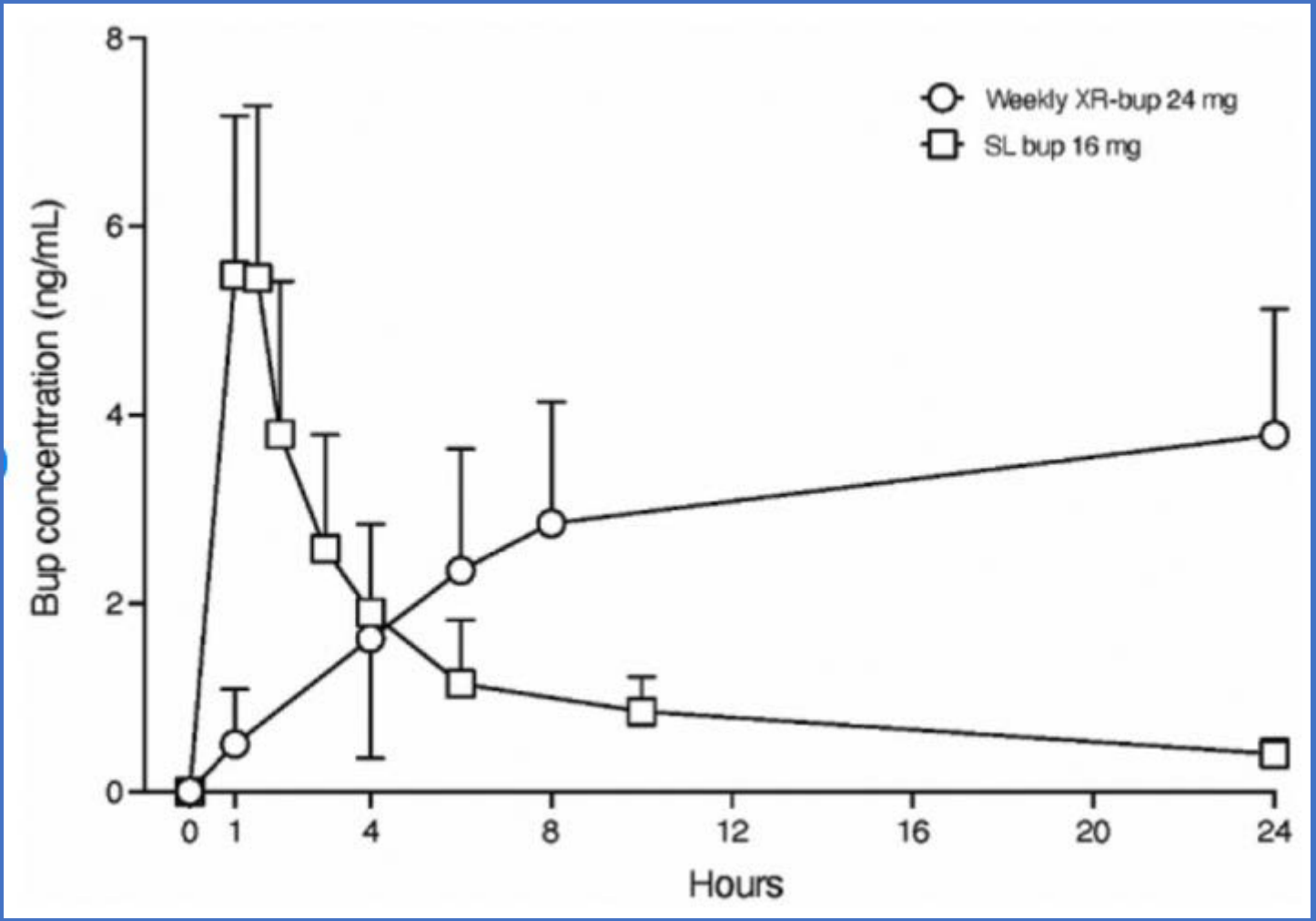
As many patients are unable to successfully taper off buprenorphine, the medical community must work to address any barriers to long-term maintenance

Ritvo et. Al, 2020

- Case Report
- Transition sublingual bup à Monthly XR bup 100mg x1 à opioid-free

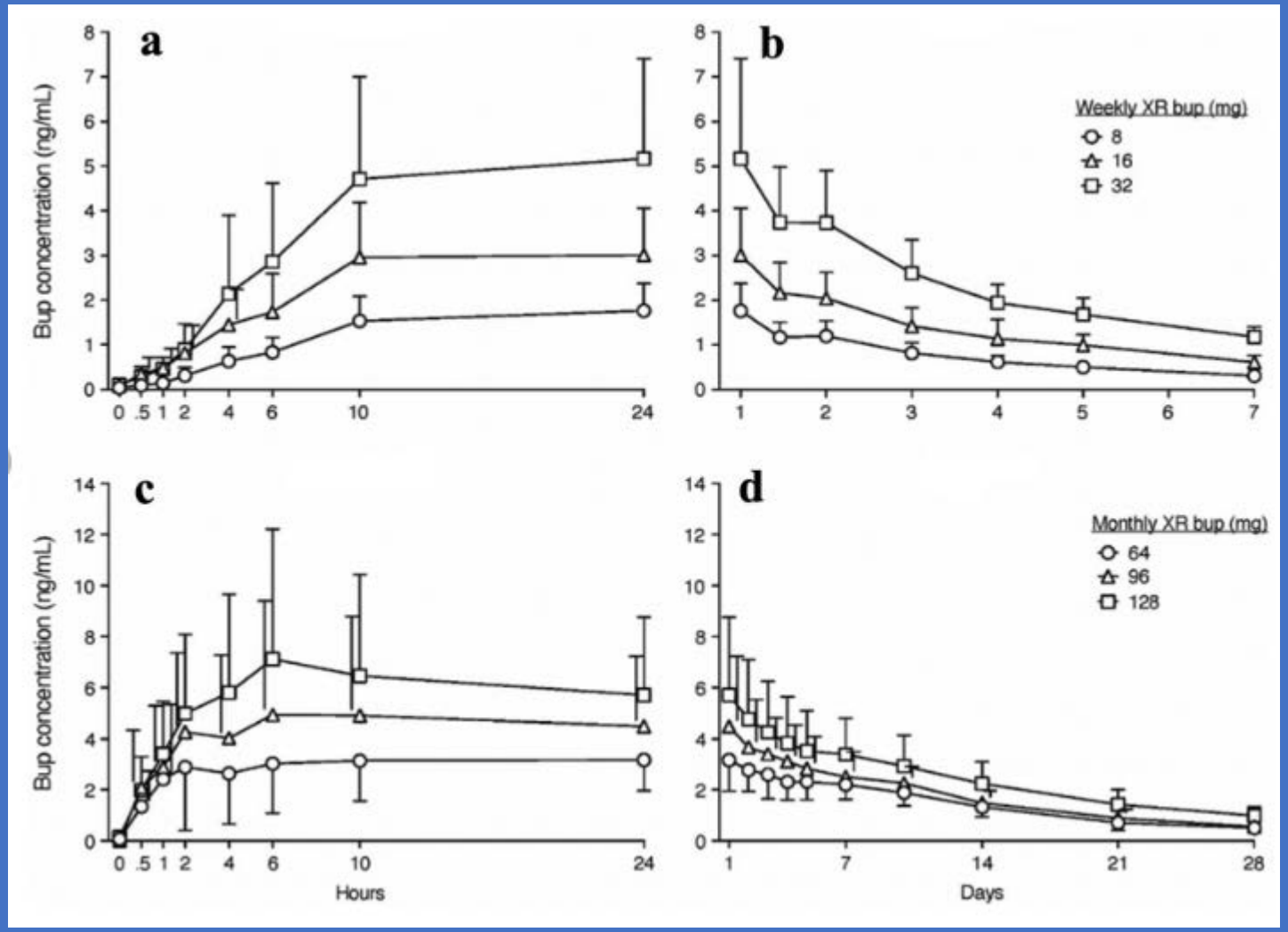
- Case 1 – from SL bup 4mg à XR bup 100mg
  - "a slight, not intolerable, malaise" in 1st two weeks
  - Followed monthly à no opioid relapse or withdrawal symptomology
- Case 2 – from SL bup 6mg à XR bup 100mg
  - "zero withdrawal symptoms"
  - "only a little pain at the injection site"
- Case 3 – SL bup 6mg à XR bup 100mg
  - Some nausea/vomiting before + after injection
  - "Once I had the shot, I had no withdrawal symptoms"

Plasma Concentrations: Sublingual bup vs Weekly XR-bup



Lowfall et. Al

Plasma Concentrations: Weekly XR bup vs Monthly XR bup



Lowfall et. Al

Tapering Methadone

Calsyn et. Al 2006

- Longitudinal Study
- Primary outcome = successful taper off methadone

- 5 year study period (1997-2002)
- Of 216 records reviewed, 30 had attempted taper
- Mean number of months in treatment = 41.4 months

- 4 patients (13.3%) successfully switched to buprenorphine, one of whom tapered off buprenorphine
- 20 patients stopped their tapers for the following reasons:
  - Unstable/withdrawal symptoms, return to drug use, psychiatric instability

No patient successfully completed methadone taper

Nosyk et. Al 2012

- Population-based retrospective cohort study
- Primary outcome = sustained successful taper (no treatment re-entry, opioid-related hospitalization or mortality within 18 months)

- 25,454 episodes reviewed from 1996-2006
- 14,602 attempted taper
- 4.4% success rate (646/14,602) among all episodes initiating a taper
  - Tapers lasting 12–52 weeks were 3.58 times more successful than those lasting <12 weeks
  - Tapers lasting >52 weeks were 6.7 times more likely to result in sustained success

The majority of patients attempting taper from methadone maintenance treatment will not succeed. Success is enhanced by gradual dose reductions interspersed with periods of stabilization

Deprescribing Benzodiazepines/Z-drugs

Overview

- In 2019, 92 million benzodiazepine prescriptions were dispensed in US
  - ~50% prescribed for >2 months

- Long-term use associated with:
  - Physical dependence and addiction
  - Memory disturbances
  - Falls and fractures
  - Increased depression
  - Impaired sleep
  - Delirium
  - 60-80% increase in risk of motor vehicle accidents
  - Potentially increased mortality
    - 2016 observational study finding users had 43% increased risk of mortality

FDA

- Black Box warning in 2020
- Re-emphasized for all marketed benzodiazepines the risk of physical dependence, addiction and withdrawal effects
- Also noted that withdrawal syndromes can persist for >12 months after cessation

Highest Risk for adverse effects

- Age >65yo
- More than one benzodiazepine or Z-drug
- Combination with opioids or gabapentinoids
- Fall risk
- COPD or respiratory disease
- Substance Use Disorder
- History of overdose
- Pregnant women

Beneficial effects of deprescribing

- Improvement in anxiety
- Improved psychomotor and cognitive function
- Reductions in:
  - Risk of falls and fractures
  - Motor Vehicle Accidents
  - Drug interactions

Risk of Withdrawal

Duration of BZD use	Frequency of BZD use	Total daily BZD dose	Risk of clinically significant withdrawal*
Any	≤ 3 days per week	Any	No
< 1 month	≥ 4 days per week	Any	Lower risk, but possible
1–3 months	≥ 4 days per week	Low†	Lower risk, but possible
1–3 months	≥ 4 days per week	Moderate‡ to high§	Yes, with greater risk with increasing dose and duration
≥ 3 months	≥ 4 days per week	Any	Yes, with greater risk with increasing dose and duration

Withdrawal Symptoms

- **58-100% of patients using for >1yr will experience withdrawal**

- 32% with long-half-life benzodiazepines are unable to stop due to withdrawal
- 42% with short-half-life benzodiazepines are unable to stop due to withdrawal

- Short-acting are associated with more severe acute withdrawal
  - All types can have protracted withdrawal

- Withdrawal develops 1-2 days after stopping short-acting benzodiazepines
  - Several days for longer-acting medications

Withdrawal Symptoms

Physical

- General (i.e. sweating)
- Neuromuscular (i.e. paresthesia)
- Sleep (i.e. insomnia)
- Sensory (i.e. Electric shock sensations)
- Cardiovascular (i.e. tachycardia)
- GI (i.e. nausea/vomiting)
- Neurologic (i.e. seizures)
- Cognitive (i.e. confusion)

Psychological

- Affective
  - Agoraphobia, depression, panic
- Behavioral
  - Restlessness
- Psychotic
  - Delirium, hallucinations

Brandt et. Al 2024

- Meta-analysis

- 113 documents offering guidance on Benzodiazepines/Z-drugs (BZD/BZRA) use were data-charted
- N = 18 were sufficiently specific and complete to consider as de-prescribing focused documents

- Interpretation:
  - BZD and BZRA NOT being used routinely as first-line pharmacologic agents
  - Restrict duration to "short-term" use (<4 weeks)
  - Lack of consistency in recommendations for specific drug, dosing and administration pattern
  - Recommend gradual dose reductions and patient shared decision-making
  - Approaches towards dose-tapering differed substantially

ASAM Clinical Guidelines 2025

- American Society of Addiction Medicine (ASAM) partnered with 9 other medical societies to provide guidance on evidence-based strategies for tapering benzodiazepine (BZD) medication across a variety of settings
- Systematic literature review

- Interpretation:
  - Engage in ongoing risk–benefit assessment of BZD use/tapering
  - Shared decision-making strategies in collaboration with patients
  - Clinicians should NOT discontinue BZDs abruptly in patients who are likely to be physically dependent and at risk of withdrawal
  - Tailor tapering strategies to each patient and adjust tapering based on patient response
  - Offer patients adjunctive psychosocial interventions to support successful tapering

Additional Research

- Initiating the offer of deprescribing via tailored letter from a PCP is effective in 25% of patients

- Study where PCP provided an education intervention directly with patients, 45% of patients were able to stop benzodiazepines in 12 months

Additional Recommendations

- Person's physical and psychologic health and personal circumstances should be stable upon taper initiation
- People who do not wish to stop benzodiazepines or z-drugs should not be pressured to do so
- Mixed views switching to a longer-acting benzodiazepine
- Z-drugs – direct tapering from these medications more sensible than switch to diazepam

Deprescribing Antidepressants

Overview

- 1 in 6 people in western countries are prescribed an antidepressant in any given year
  - Median duration of use: > 5 years in the US
  - 30-50% of patients without evidence-based reasons for continued prescription

- Adverse Effects of Use
  - Emotional Numbing (71%)
  - Sexual Side Effects – 25-80% of patients
    - Can persist even after cessation (post-SSRI sexual dysfunction)
  - 34% increased risk of dementia (case control study of 225,000 patients on antidepressant for >3yrs)
  - Increase falls - 2.2% increase compared to controls
  - Bleeding Risk - 55% greater risk of UGIB compared to those not on SSRIs (meta-analysis of 22 studies)

Antidepressants

- Estimated 1000 studies on starting antidepressants
- Only 20 studies on discontinuing

All classes of antidepressants are associated with physical dependence

Tricyclics (TCAs)
Monoamine Oxidase Inhibitors (MAO-Is)
Selective Serotonin Reuptake Inhibitors (SSRIs)
Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Withdrawal

- 2019 systematic review of 14 studies
  - Antidepressant withdrawal incidences ranged from 27-86%; median 55%
- Risk of withdrawal increases after only 4-6 weeks of daily use
- For patients taking antidepressants for >3 years, ~1/2 will experience severe withdrawal symptoms
- Most severe withdrawal associated with:
  - Paroxetine
  - Duloxetine
  - Venlafaxine
  - Mirtazapine

Antidepressant Withdrawal

- Withdrawal symptoms
  - Dizziness (65%)
  - Headache (53%)
  - Fatigue (45%)
  - Confusion (53%)
  - Memory Difficulty (34%)
  - Nausea (44%)
  - Irritability (60%)
  - Myoclonus, hyperesthesia, tremor, vivid dreams, sleep disturbances, depressed mood

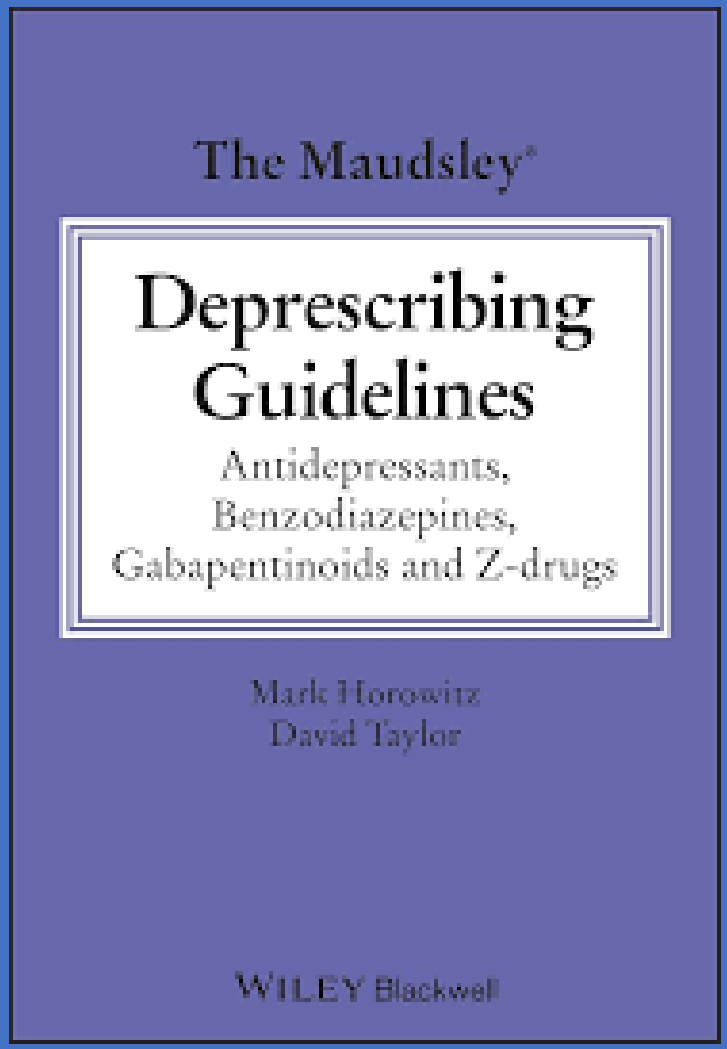
- Brain ‘zaps’ - Head sensation often experienced on lateral eye movements
  - **Considered pathognomonic for withdrawal**

Risk of Relapse

- Meta-analysis
  - Discontinuing antidepressants increases the chance of relapse only when it is conducted rapidly (<8 weeks)

- In studies where tapering is conducted over longer periods (up to 6 months)
  - No increased chance of relapse compared to continuation of antidepressants

- Tapering guidance on individual medications
  - Antidepressants
  - Benzodiazepines
  - Z-drugs
  - Gabapentinoids



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